ФББ
НИУ ВШЭ

Научно-учебная группа «Изучение биологии рака на модели опухолевых органоидов»

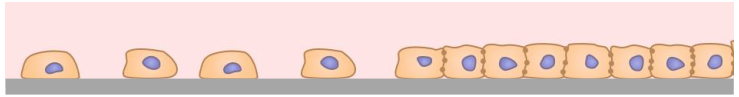
Москва
2025

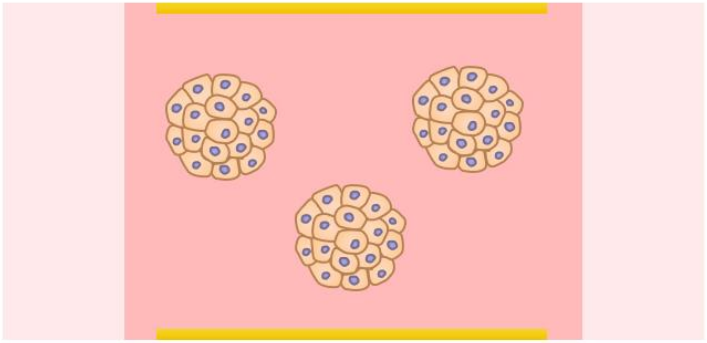
Опухолевые органоиды: Модель для изучения рака или будущее клинической онкологии?

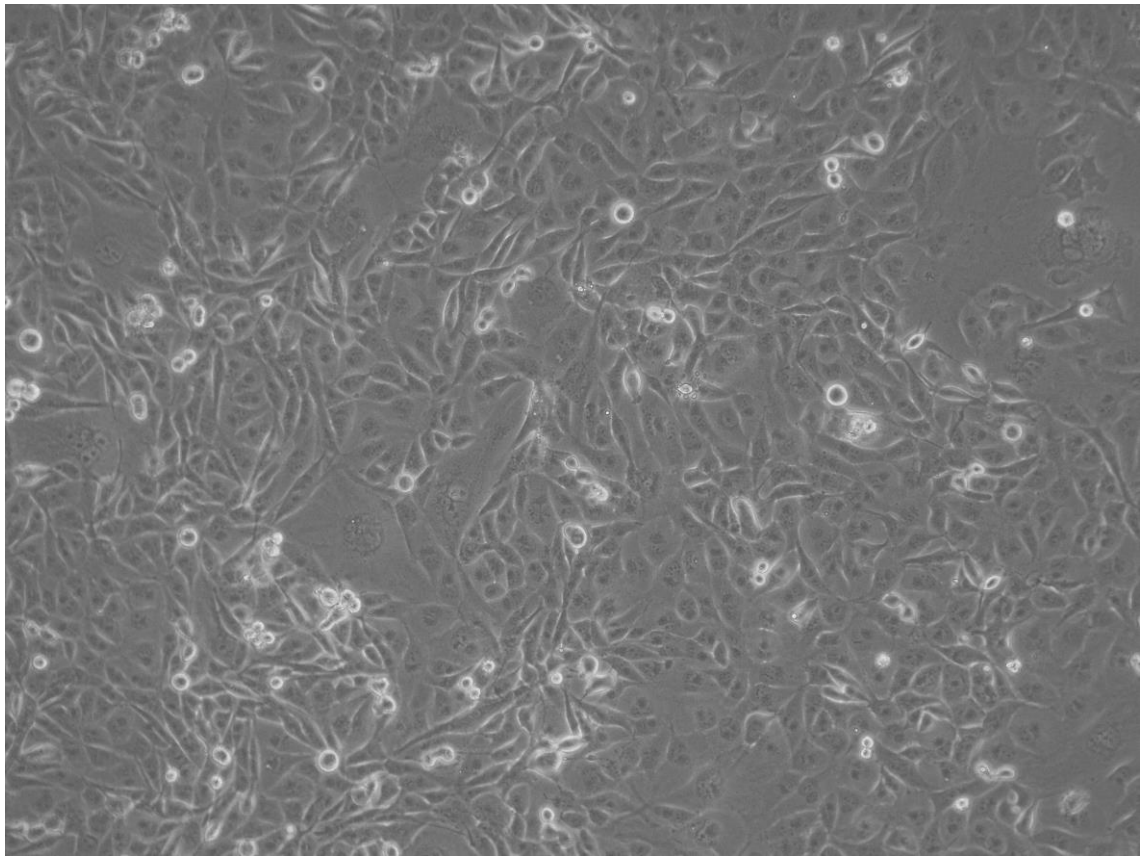
Никулин Сергей Вячеславович, к.б.н.

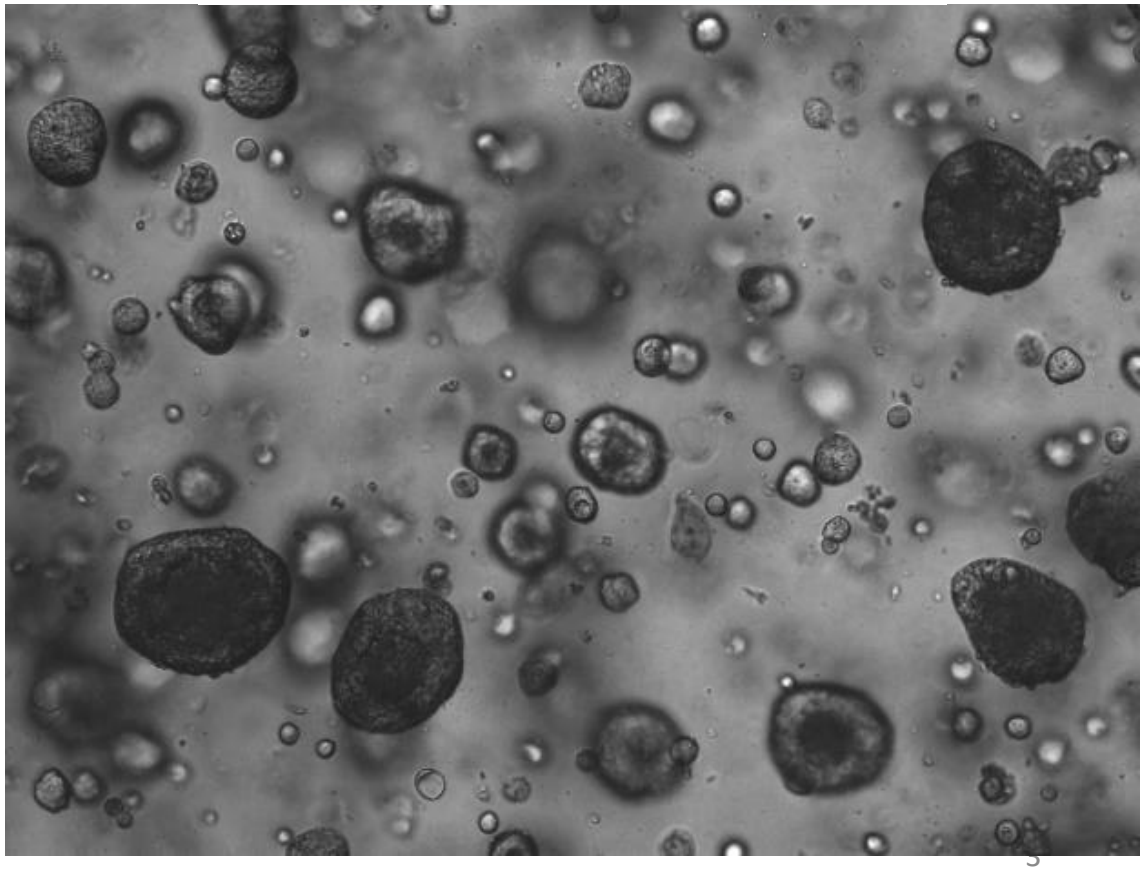
Опухолевые органоиды

2D против 3D







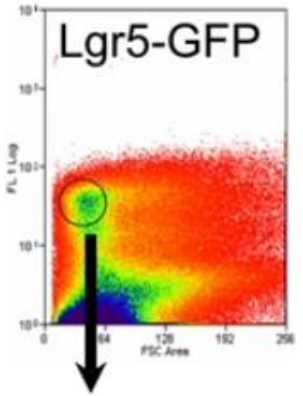


Органоиды

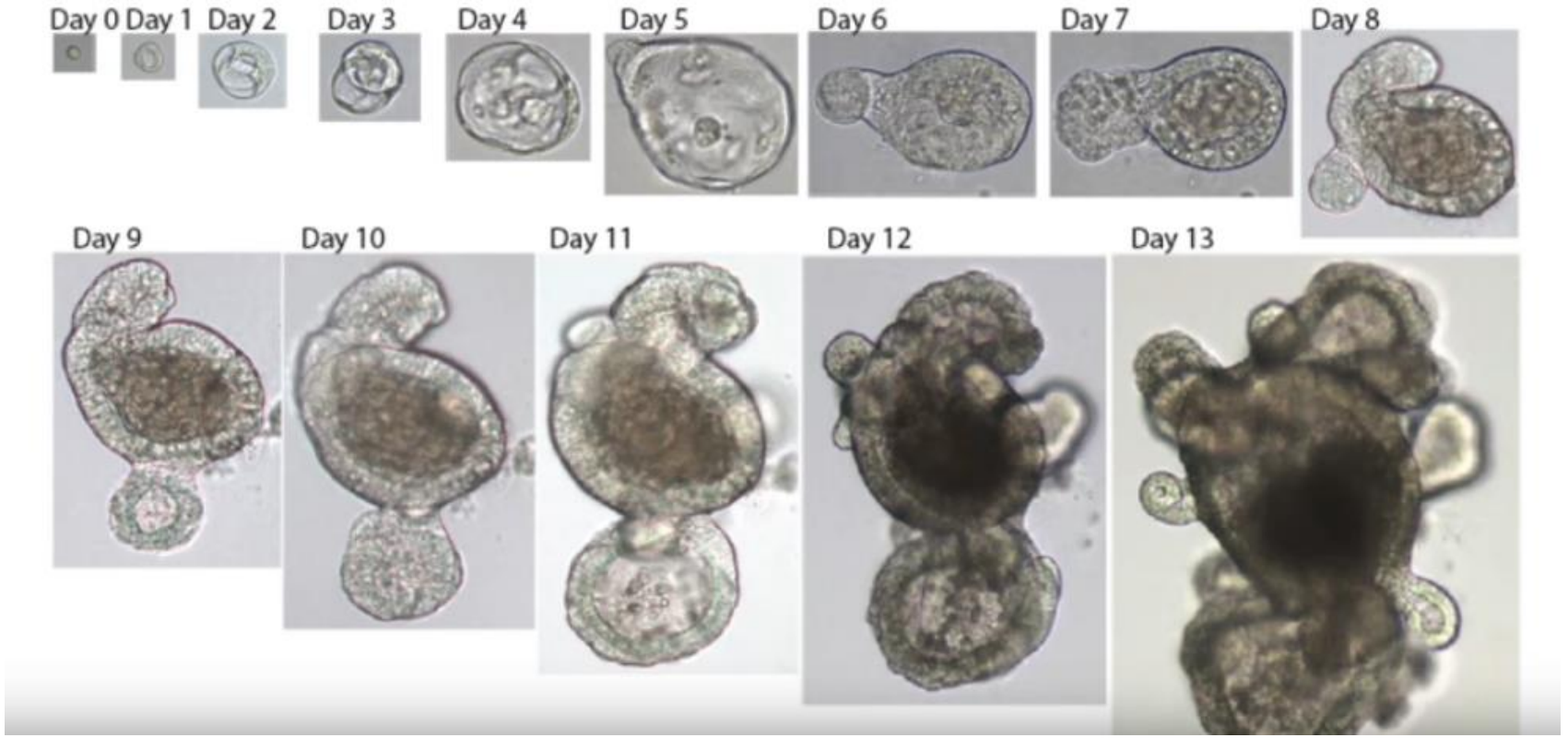
Toshiro Sato

Hans Clevers

Single Lgr5 cells form mini-guts in 3D-culture



- R-spondin1 (Wnt agonist)
- EGF
- Noggin (BMP inhibitor)
- Matrigel



Sato T. et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche //Nature. – 2009. – Т. 459. – №. 7244. – С. 262-265.

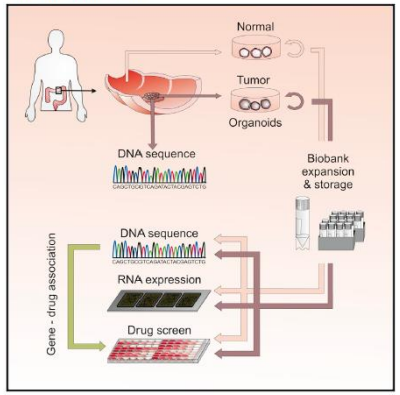
Опухолевые органоиды (тумороиды)

Resource

Cell

Prospective Derivation of a Living Organoid Biobank of Colorectal Cancer Patients

Graphical Abstract



Authors
Marc van de Wetering, Hayley E. Francies, ..., Mathew J. Garnett, Hans Clevers

Correspondence
mg12@sanger.ac.uk (M.J.G.), h.clevers@hubrecht.eu (H.C.)

In Brief
3D organoid cultures derived from healthy and tumor tissue from colorectal cancer patients are used for a high throughput drug screen to identify gene-drug associations that may facilitate personalized therapy.

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11867-6 OPEN

Patient-derived lung cancer organoids as in vitro cancer models for therapeutic screening

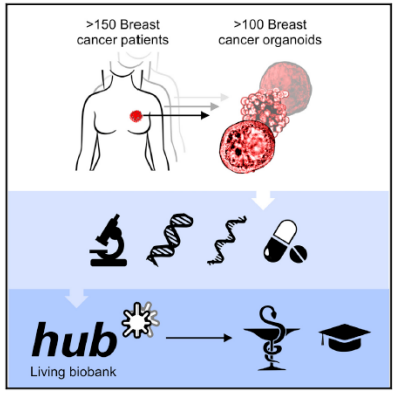
Minsuh Kim[1], Hyemin Mun[1], Chang Oak Sung[1,2], Eun Jeong Cho[1], Hye-Joon Jeon[1], Sung-Min Chun[1,2], Da Jung Jung[3], Tae Hoon Shin[3], Gi Seok Jeong[3], Dong Kwan Kim[4], Eun Kyung Choi[5], Seong-Yun Jeong[5], Alison M. Taylor[6], Sejal Jain[6], Matthew Meyerson[6] & Se Jin Jang[1,2]

Resource

Cell

A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity

Graphical Abstract



Authors
Norman Sachs, Joep de Ligt, Oded Kopper, ..., Robert Gerhardus Jacob Vries, Edwin Cuppen, Hans Clevers

Correspondence
h.clevers@hubrecht.eu

In Brief
The heterogeneity of breast cancer subtypes can be captured using organoid cultures that can facilitate drug screens that corroborate with patient responses.

Please cite this article in press as: Boj et al., Organoid Models of Human and Mouse Ductal Pancreatic Cancer, Cell (2015), http://dx.doi.org/10.1016/j.cell.2014.12.021

Resource

Cell

Organoid Models of Human and Mouse Ductal Pancreatic Cancer

Sylvia F. Boj,[1,2,14] Chang-Il Hwang,[3,4,14] Lindsey A. Baker,[3,4,14] Iok In Christine Chio,[3,4,14] Dannielle D. Engle,[3,4,14] Vincenzo Corbo,[3,4,14] Myrthe Jager,[1,14] Mariano Ponz-Sarvise,[3,4] Hervé Tiriac,[3,4] Mona S. Spector,[3,4] Ana Gracanin,[1,2] Tobiloba Oni,[3,4,5] Kenneth H. Yu,[3,4,6,7] Ruben van Boxtel,[1] Meritxell Huch,[1,15] Keith D. Rivera,[3] John P. Wilson,[3] Michael E. Feigin,[3,4] Daniel Öhlund,[3,4] Abram Handly-Santana,[4,8] Christine M. Ardito-Abraham,[3,4] Michael Ludwig,[3,4] Ela Elyada,[3,4] Brinda Alagesan,[3,4,9] Giulia Biffi,[3,4] Georgi N. Yordanov,[4,8] Bethany Delcuze,[3,4] Brianna Creighton,[3,4] Kevin Wright,[3,4] Youngkyu Park,[3,4] Folkert H.M. Morsink,[10] I. Quintus Molenaar,[11] Inne H. Borel Rinkes,[11] Edwin Cuppen,[1] Yuan Hao,[3] Ying Jin,[3] Isaac J. Nijman,[1] Christine Iacobuzio-Donahue,[6] Steven D. Leach,[6] Darryl J. Pappin,[3] Molly Hammell,[3] David S. Klimstra,[12] Olca Basturk,[12] Ralph H. Hruban,[13] George Johan Offerhaus,[10] Robert G.J. Vries,[1,2] Hans Clevers,[1,*] and David A. Tuveson[3,4,6,*]

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 5, 1410–1426
doi:10.1210/clinem/dgab020
Clinical Research Article

ENDOCRINE SOCIETY OXFORD

nature medicine RESOURCE
https://doi.org/10.1038/s41591-019-0422-6

https://doi.org/10.1038/s41591-019-0422-6

An organoid platform for ovarian cancer captures intra- and interpatient heterogeneity

Oded Kopper[1,2], Chris J. de Witte[3,15], Kadi Lõhmussaar[1,2,15], Jose Espejo Valle-Inclan[3,15], Nizar Hami[2,4], Lennart Kester[1,2], Anjali Vanita Balgobind[1,2], Jeroen Korving[1,2], Natalie Proost[5], Harry Begthel[1,2], Lise M. van Wijk[6], Sonia Aristín Revilla[1,2], Rebecca Theeuwsen[5], Marieke van de Ven[5], Markus J. van Roosmalen[3], Bas Ponsioen[2,4], Victor W. H. Ho[7], Benjamin G. Neel[7,8], Tjalling Bosse[9], Katja N. Gaarenstroom[10], Harry Vrieling[6], Maaike P. G. Vreeswijk[6], Paul J. van Diest[11], Petronella O. Witteveen[12], Trudy Jonges[11], Johannes L. Bos[2,4], Alexander van Oudenaarden[1,2], Ronald P. Zweemer[13], Hugo J. G. Snippert[2,4], Wigard P. Kloosterman[3*] and Hans Clevers[1,2,14*]

Clinical Research Article

Organoid Cultures Derived From Patients With Papillary Thyroid Cancer

Dong Chen,[1,3*] Yawen Tan,[2*] Zhichao Li,[1] Wujiao Li,[1] Lei Yu,[1] Wei Chen,[1] Yuchen Liu,[1] Lisa Liu,[1] Liangfeng Guo,[2] Weiren Huang,[1,3] and Yongsheng Zhao[1,4]

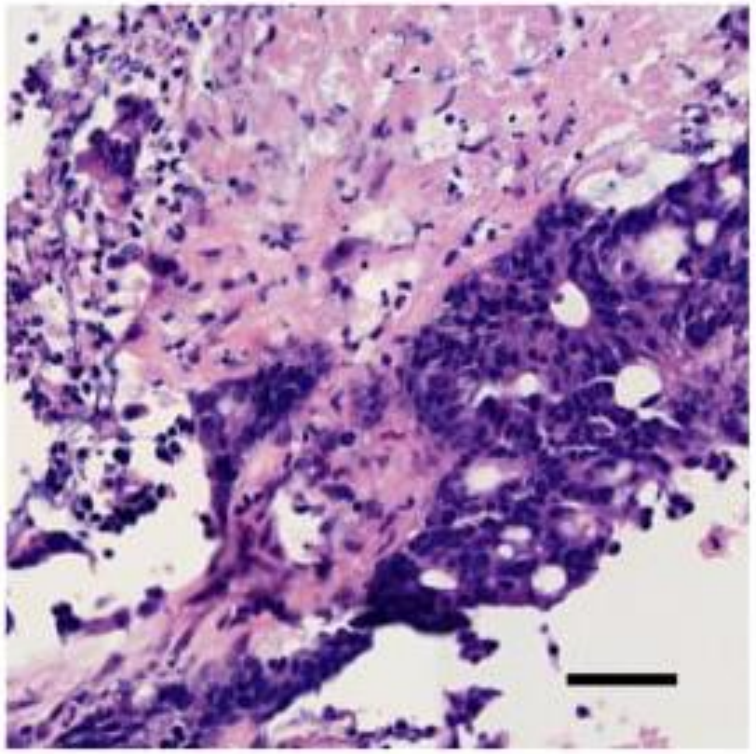
[1]Institute of Shenzhen Translational Medicine, Shenzhen Second People's Hospital, the First Affiliated Hospital of Shenzhen University, Shenzhen 518035, Guangdong, China; [2]Department of Breast and Thyroid Surgery, Shenzhen Second People's Hospital, Shenzhen 518035, Guangdong, China; [3]Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, Guangdong, China; and [4]Department of Nuclear Medicine, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong, China

ORCiD number: 0000-0001-5432-2847 (Y. Zhao).

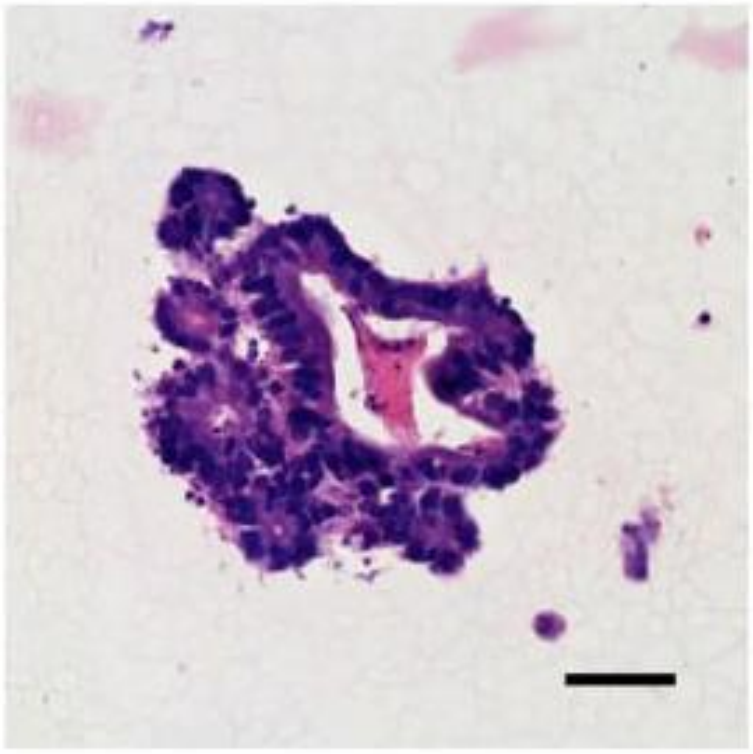
*Dong Chen and Yawen Tan contributed equally to this work.

Опухолевые органоиды (тумороиды)

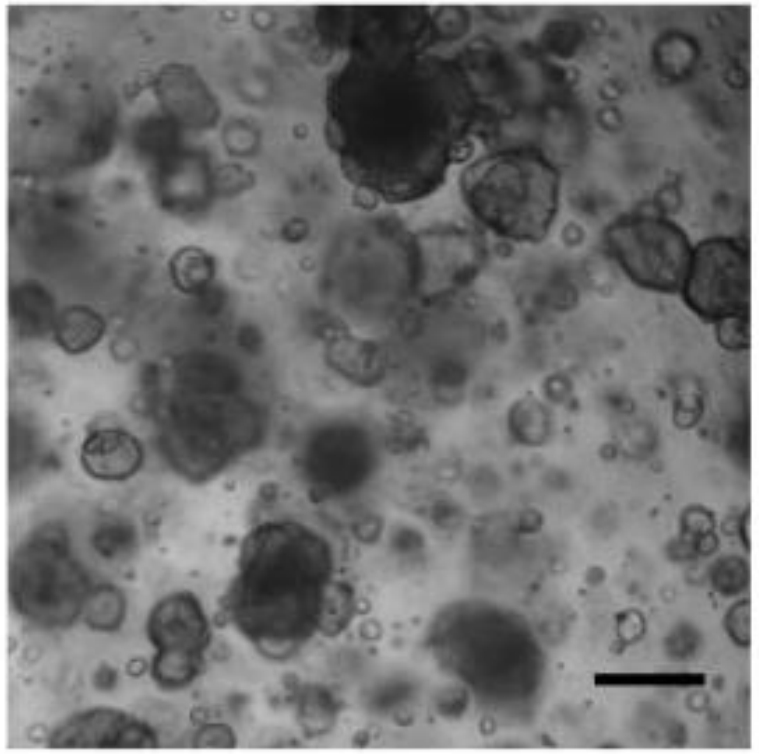
Tumor Tissue
H&E



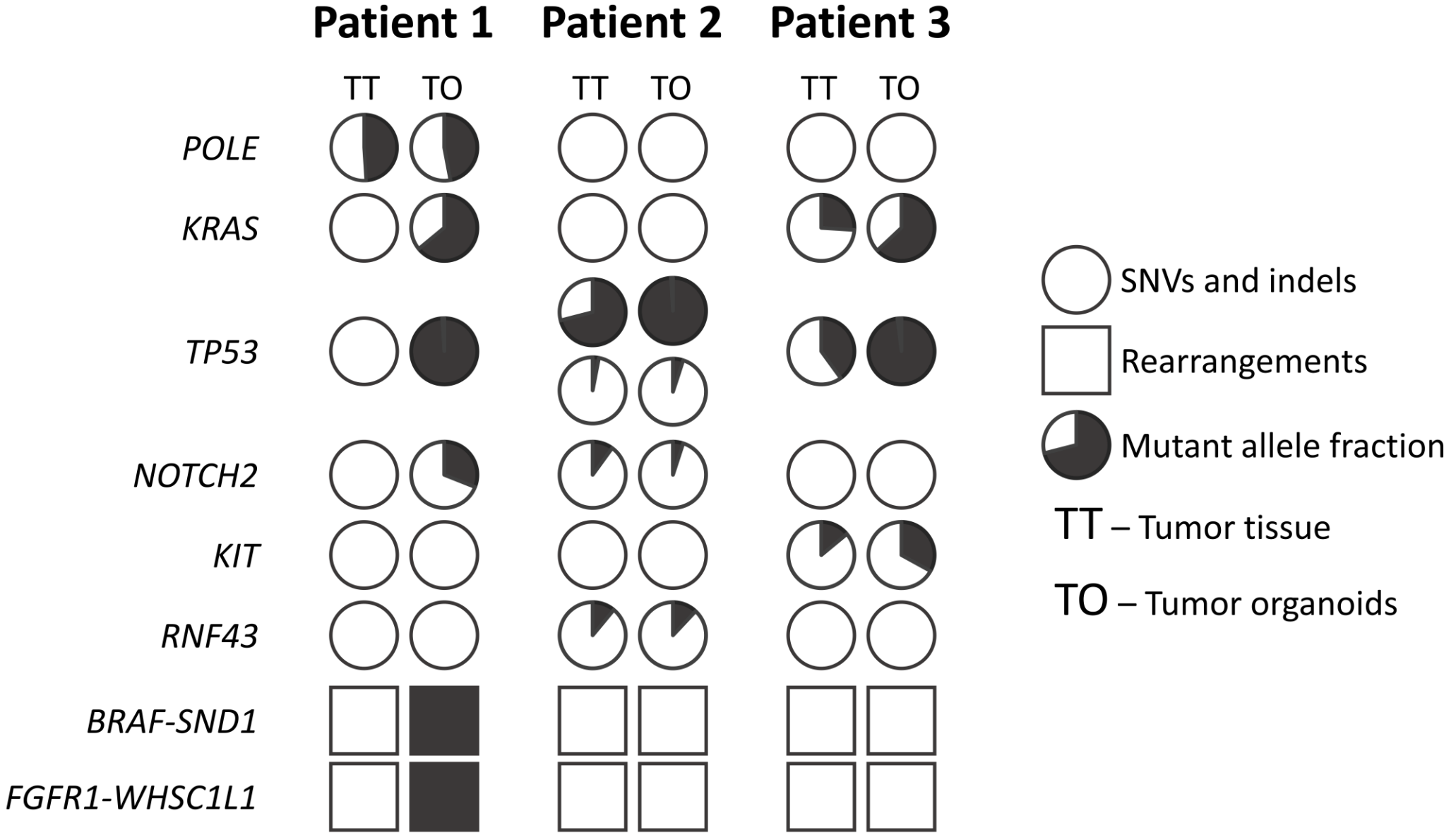
Tumor Organoids
H&E



Tumor Organoids
Brightfield



Опухолевые органоиды (тумороиды)



Клинические исследования

Клинические исследования

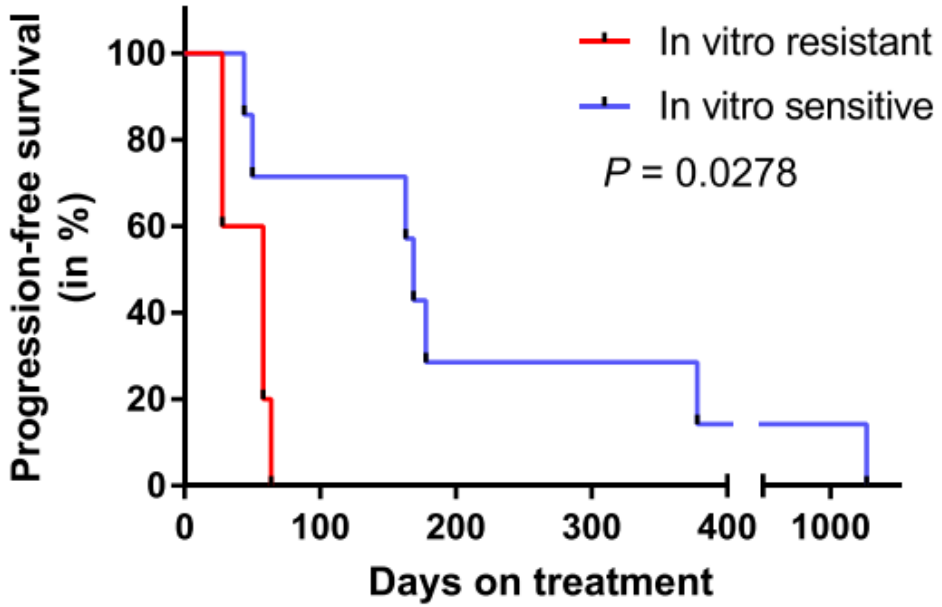
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Patient-derived organoids can predict response to chemotherapy in metastatic colorectal cancer patients

Salo N. Ooft[1,2]*, Fleur Weeber[1,2]*, Krijn K. Dijkstra[1,2†], Chelsea M. McLean[1,2†], Sovann Kaing[1,2], Erik van Werkhoven[3], Luuk Schipper[1,2], Louisa Hoes[1,2], Daniel J. Vis[2,4], Joris van de Haar[1,2,4], Warner Prevoo[5], Petur Snaebjornsson[6], Daphne van der Velden[1,2‡], Michelle Klein[1,2], Myriam Chalabi[1], Henk Boot[7], Monique van Leerdam[7], Haiko J. Bloemendal[8], Laurens V. Beerepoot[9], Lodewyk Wessels[2,4,10], Edwin Cuppen[2,11,12], Hans Clevers[2,13,14], Emile E. Voest[1,2,7§]

There is a clear and unmet clinical need for biomarkers to predict responsiveness to chemotherapy for cancer. We developed an in vitro test based on patient-derived tumor organoids (PDOs) from metastatic lesions to identify nonresponders to standard-of-care chemotherapy in colorectal cancer (CRC). In a prospective clinical study, we show the feasibility of generating and testing PDOs for evaluation of sensitivity to chemotherapy. Our PDO test predicted response of the biopsied lesion in more than 80% of patients treated with irinotecan-based therapies without misclassifying patients who would have benefited from treatment. This correlation was specific to irinotecan-based chemotherapy, however, and the PDOs failed to predict outcome for treatment with 5-fluorouracil plus oxaliplatin. Our data suggest that PDOs could be used to prevent cancer patients from undergoing ineffective irinotecan-based chemotherapy.



RESEARCH

ORGANOIDS

Patient-derived organoids model treatment response of metastatic gastrointestinal cancers

Georgios Vlachogiannis,[1] Somaieh Hedayat,[1] Alexandra Vatsiou,[2] Yann Jamin,[3] Javier Fernández-Mateos,[1,2] Khurum Khan,[1,4] Andrea Lampis,[1] Katherine Eason,[1] Ian Huntingford,[1] Rosemary Burke,[5] Mihaela Rata,[3] Dow-Mu Koh,[3,6] Nina Tunariu,[3,6] David Collins,[3] Sanna Hulkki-Wilson,[1] Chanthirika Ragulan,[1] Inmaculada Spiteri,[2] Sing Yu Moorcraft,[4] Ian Chau,[4] Sheela Rao,[4] David Watkins,[4] Nicos Fotiadis,[6] Maria Bali,[3,6] Mahnaz Darvish-Damavandi,[1] Hazel Lote,[1,4] Zakaria Eltahir,[1] Elizabeth C. Smyth,[4] Ruwaida Begum,[4] Paul A. Clarke,[5] Jens C. Hahne,[1] Mitchell Dowsett,[7] Johann de Bono,[8] Paul Workman,[5] Anguraj Sadanandam,[1] Matteo Fassan,[9] Owen J. Sansom,[10] Suzanne Eccles,[5] Naureen Starling,[4] Chiara Braconi,[4,5] Andrea Sottoriva,[2] Simon P. Robinson,[3] David Cunningham,[4] Nicola Valeri[1,4]*

Patient-derived organoids (PDOs) have recently emerged as robust preclinical models; however, their potential to predict clinical outcomes in patients has remained unclear. We report on a living biobank of PDOs from metastatic, heavily pretreated colorectal and gastroesophageal cancer patients recruited in phase 1/2 clinical trials. Phenotypic and genotypic profiling of PDOs showed a high degree of similarity to the original patient tumors. Molecular profiling of tumor organoids was matched to drug-screening results, suggesting that PDOs could complement existing approaches in defining cancer vulnerabilities and improving treatment responses. We compared responses to anticancer agents ex vivo in organoids and PDO-based orthotopic mouse tumor xenograft models with the responses of the patients in clinical trials. Our data suggest that PDOs can recapitulate patient responses in the clinic and could be implemented in personalized medicine programs.

sequencing studies of primary CRC (*11*) or gastro-esophageal cancer (GOC) (*12*) was applied in our cohort, we found no correlation between PDO take-up rate and tumor percentage, suggesting that PDOs can also be established in cases of a low tumor/stroma ratio, thus allowing the ex vivo expansion of the cancer population in samples that would have otherwise failed quality-control tests for next-generation sequencing (NGS).

PDOs presented in this study were derived from ultrasound (n = 20), computed tomography (CT)–guided (n = 7), or endoscopic (n = 2) biopsies of metastatic CRC (mCRC; n = 16), metastatic GOC (mGOC; n = 4), and metastatic cholangiocarcinoma (n = 1) patients (fig. S1). Liver, pelvic, peritoneal, and nodal metastases of chemorefractory patients were used to establish PDOs. In several cases, PDOs were established from sequential biopsies at baseline (BL), at the time of best response [partial response (PR) or stable disease (SD)], and at the time of disease progression (PD), as well as from multiregion biopsies (table S1).

Histological evaluation revealed notable morphological similarities between PDOs and the patient biopsies from which they were originally derived (Fig. 1, A and B, and figs. S2A and S2B). Immunohistochemistry markers routinely used in the diagnosis of CRC (CDX-2 and CK7) showed that the parental tumor's expression pattern was maintained in PDOs, even when derived from sequential biopsies during treatment (fig. S2, C to E). Similarly, amplification of oncogenic drivers such as *ERBB2* (Fig. 1C and fig. S2F) and re-

		Response in the Clinic		
		R	NR	
Ex Vivo Sensitivity	S	7	1*	8
	NS	0	13	10
		7	14	21

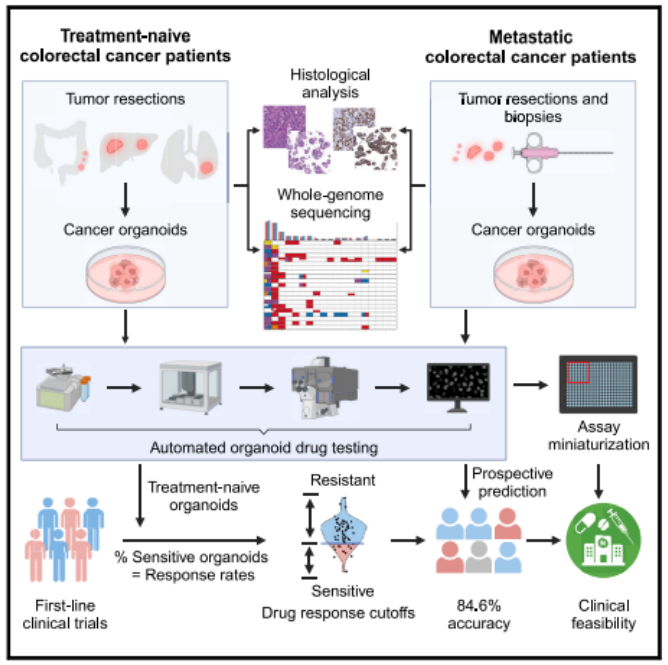
Клинические исследования

Cell Reports
Medicine

Article

Unified framework for patient-derived, tumor-organoid-based predictive testing of standard-of-care therapies in metastatic colorectal cancer

Graphical abstract



Authors

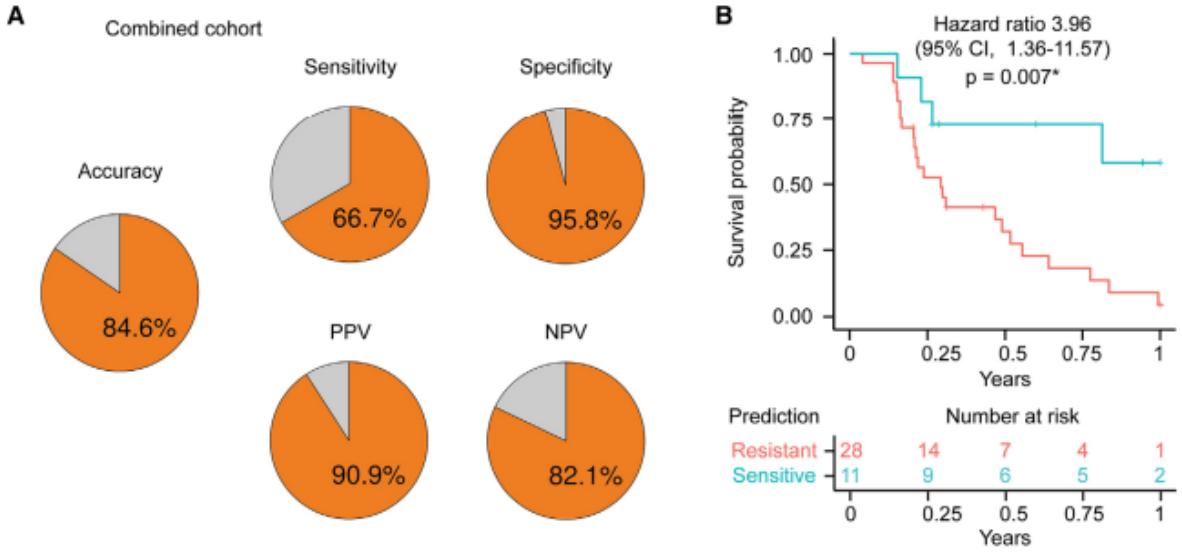
Tao Tan, Dmitri Mouradov, Margaret Lee, ..., Antony W. Burgess, Peter Gibbs, Oliver M. Sieber

Correspondence

sieber.o@wehi.edu.au

In brief

Tan et al. describe a framework for predictive tumor-organoid-based testing of standard-of-care therapies for patients with metastatic colorectal cancer, demonstrating assay accuracy and feasibility of clinical reporting. Predictive organoid drug testing can complement routine genomic marker analyses, facilitating selection of the most active agents and avoidance of ineffective treatments.



	Drug	Relative sensitivity
Ph III RCT demonstrating survival benefit	TAS102	●
	Regorafenib	●
Limited prospective data supporting rechallenge strategies	Oxaliplatin	●
	Irinotecan	●
	5FU/fluoropyrimidine	●
Limited evidence for treatment in refractory setting	Pemetrexed	●
	Gemcitabine	●
	Temozolomide	●
		Less sensitive ← Intermediate sensitivity → More sensitive

Клинические исследования

KSBMB
Korean Society for Biochemistry and Molecular Biology

www.nature.com/emm

REVIEW ARTICLE OPEN

Check for updates

Patient-derived tumor organoids: a new avenue for preclinical research and precision medicine in oncology

Lucie Thorel[1,2,9], Marion Perréard[1,3,9], Romane Florent[4,9], Jordane Divoux[1,2,4], Sophia Coffy[5], Audrey Vincent[6], Cédric Gaggioli[7], Géraldine Guasch[8], Xavier Gidrol[5], Louis-Bastien Weiswald[1,2,4,10]✉ and Laurent Poulain[1,2,4,10]✉

Over the past decade, the emergence of patient-derived tumor organoids (PDTOs) has broadened the repertoire of preclinical models and progressively revolutionized three-dimensional cell culture in oncology. PDTO can be grown from patient tumor samples with high efficiency and faithfully recapitulates the histological and molecular characteristics of the original tumor. Therefore, PDTOs can serve as invaluable tools in oncology research, and their translation to clinical practice is exciting for the future of precision medicine in oncology. In this review, we provide an overview of methods for establishing PDTOs and their various applications in cancer research, starting with basic research and ending with the identification of new targets and preclinical validation of new anticancer compounds and precision medicine. Finally, we highlight the challenges associated with the clinical implementation of PDTO, such as its representativeness, success rate, assay speed, and lack of a tumor microenvironment. Technological developments and autologous cocultures of PDTOs and stromal cells are currently ongoing to meet these challenges and optimally exploit the full potential of these models. The use of PDTOs as standard tools in clinical oncology could lead to a new era of precision oncology in the coming decade.

Experimental & Molecular Medicine (2024) 56:1531–1551; https://doi.org/10.1038/s12276-024-01272-5

Name of the study	Identifier	Estimated study completion date
Clinical trials in which principal outcome include comparison between PDTO and clinical response		
Translational Analysis In Longitudinal Series of Ovarian Cancer Organoids (TAILOR)	NCT04555473	May-23
Clinical Study on Drug Sensitivity Verification or Prediction of Therapy for Breast Cancer by Patient-Derived Organoid Model	NCT03544047	Jul-21
Drug Sensitivity Correlation Between Patient-Derived Organoid Model and Clinical Response in NSCLC Patients	NCT03453307	Jul-21
Establishing Organoids From Metastatic Pancreatic Cancer Patients, the OPT-I Study	NCT03500068	Sep-22
OPPOSITE: Outcome Prediction Of Systemic Treatment in Esophagogastric Carcinoma	NCT03429816	Aug-22
Organoid Based Response Prediction in Esophageal Cancer (RARESTEM/Org)	NCT03283527	Jan-20
Organoids in Predicting Chemoradiation Sensitivity on Rectal Cancer	NCT03577808	Nov-20
Patient-derived Organoid Model and Circulating Tumor Cells for Treatment Response of Lung Cancer	NCT03655015	Dec-22
Pharmacotyping of Pancreatic Patient-derived Organoids	NCT05196334	Dec-24
Cetuximab Sensitivity Correlation Between Patient-Derived Organoids and Clinical Response in Colon Cancer Patients.	NCT04906733	Dec-23
Study on the Consistency Evaluation of Organoids Used in the Clinical Treatment of Ovarian Cancer With Anti-tumor Drugs	NCT05175326	Nov-21
Development of a Prediction Platform for Neoadjuvant Treatment and Prognosis in Pancreatic Cancer Using Organoid	NCT04777604	Jan-26
Organoids-on-a-chip for Colorectal Cancer and in Vitro Screening of Chemotherapeutic Drugs	NCT04996355	May-24
Development of a Prediction Platform for Adjuvant Treatment and Prognosis in Resected Pancreatic Cancer Using Organoid	NCT04736043	Jan-26
Study on Consistency Evaluation for Drug Sensitivity of Patient-Derived Organoid Model From Cholangiocarcinoma Patients	NCT05634694	Dec-24
SOTO: Treatment Sensitivity of Organoids to Predict Treatment Outcome	NCT05400239	May-23
The Culture of Advanced or Recurrent Ovarian Cancer Organoids and Drug Screening	NCT05290961	Dec-24
The Culture of Ovarian Cancer Organoids and Drug Screening	NCT04768270	Dec-24
Tailoring Treatment in Colorectal Cancer (TargetCRC)	NCT05401318	Jan-27
3D Bioprinted Models for Predicting Chemotherapy Response in Colorectal Cancer With/Without Liver Metastases	NCT04755907	Dec-23

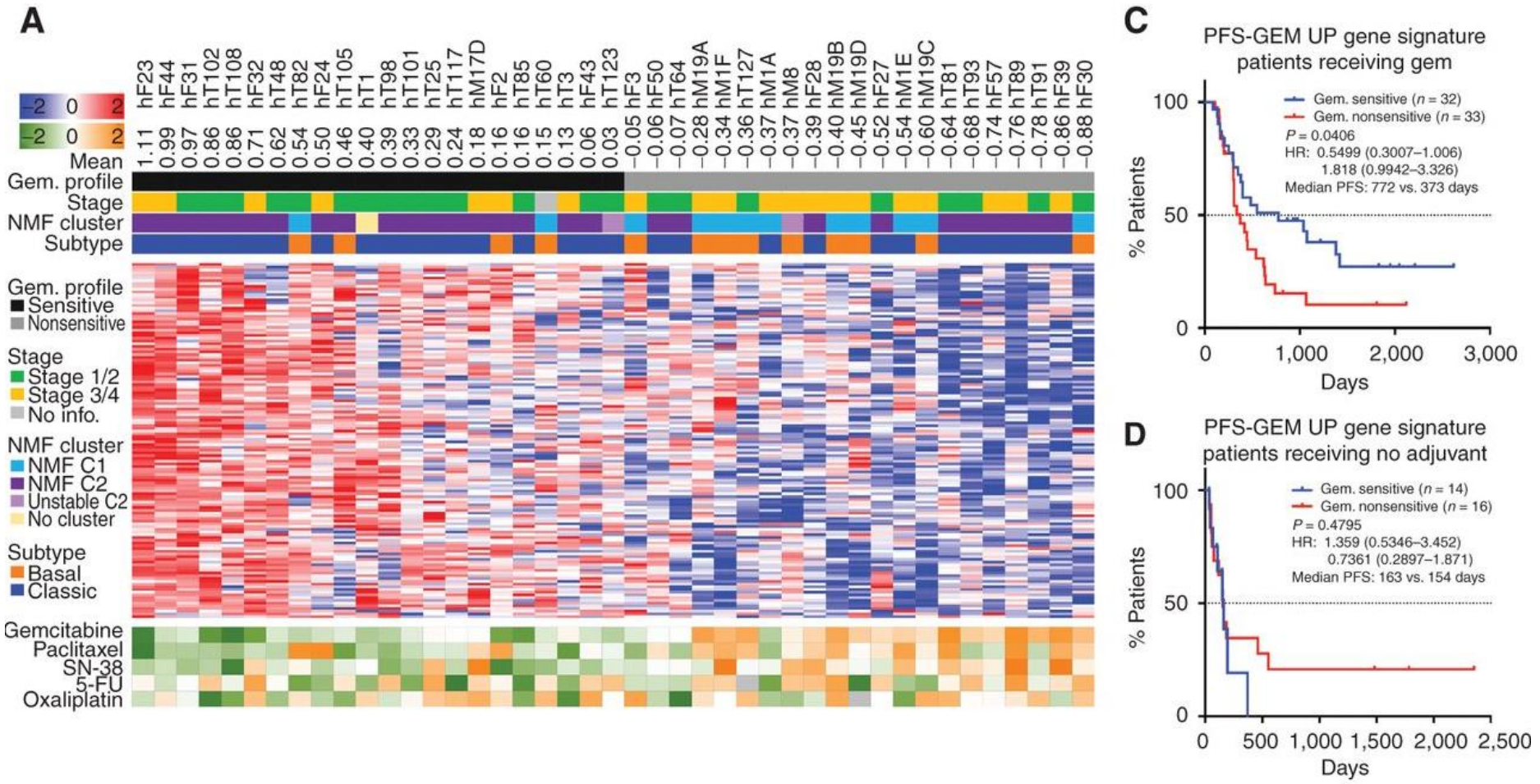
Биомаркеры

Биомаркеры

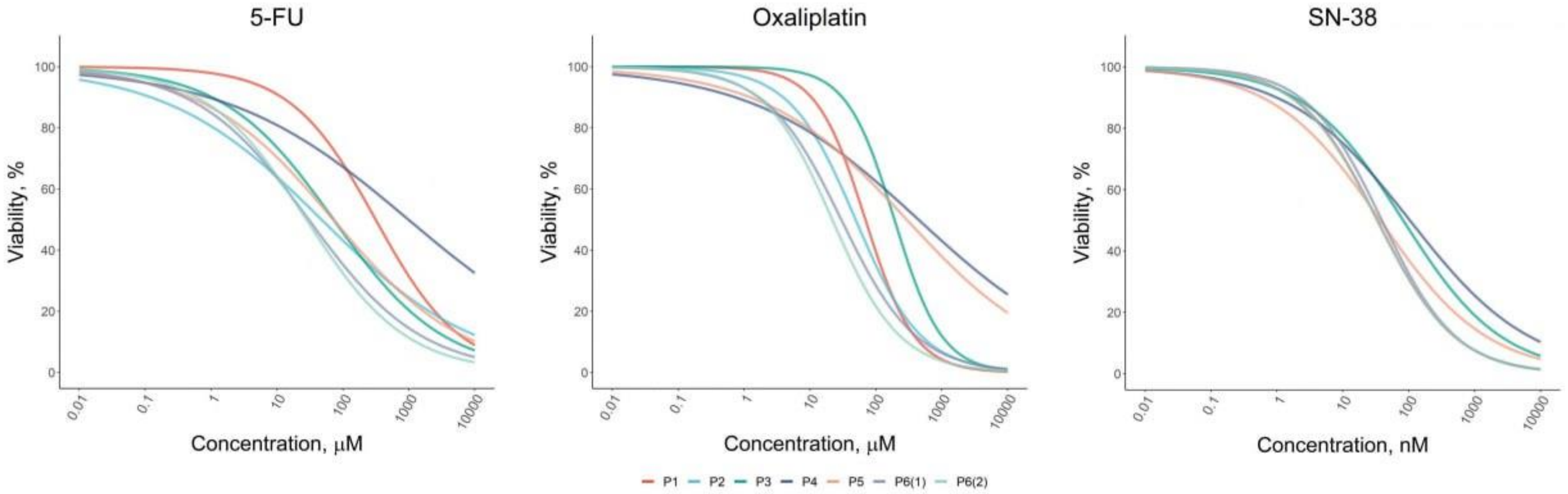
Published OnlineFirst May 31, 2018; DOI: 10.1158/2159-8290.CD-18-0349

RESEARCH ARTICLE

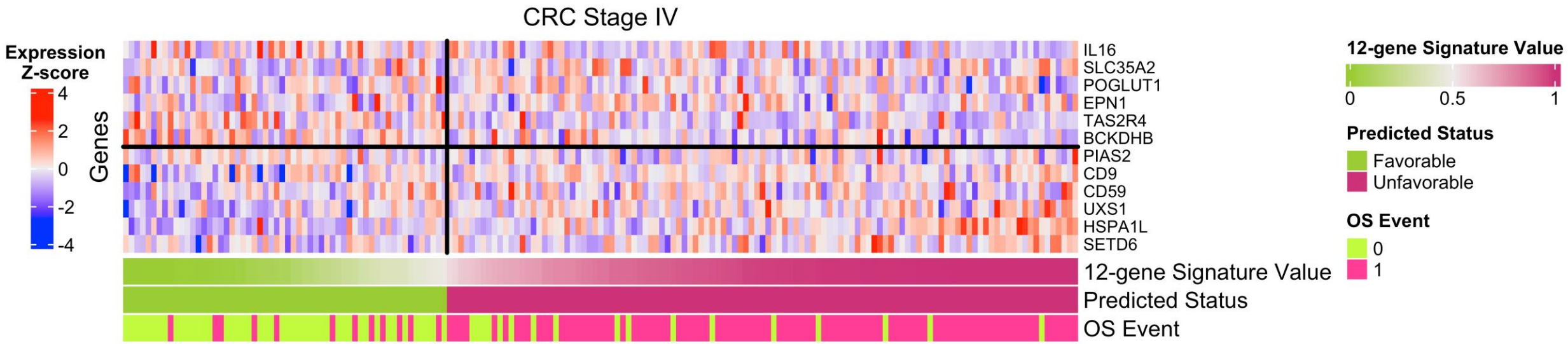
Organoid Profiling Identifies Common Responders to Chemotherapy in Pancreatic Cancer



Биомаркеры


5-FU
Oxaliplatin
SN-38
Viability, %
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
10000
Concentration, μM
Concentration, nM
P1
P2
P3
P4
P5
P6(1)
P6(2)

Биомаркеры


CRC Stage IV
Expression Z-score
4
2
0
-2
-4
Genes
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SLC35A2
POGLUT1
EPN1
TAS2R4
BCKDHB
PIAS2
CD9
CD59
UXS1
HSPA1L
SETD6
12-gene Signature Value
Predicted Status
OS Event
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Predicted Status
Favorable
Unfavorable
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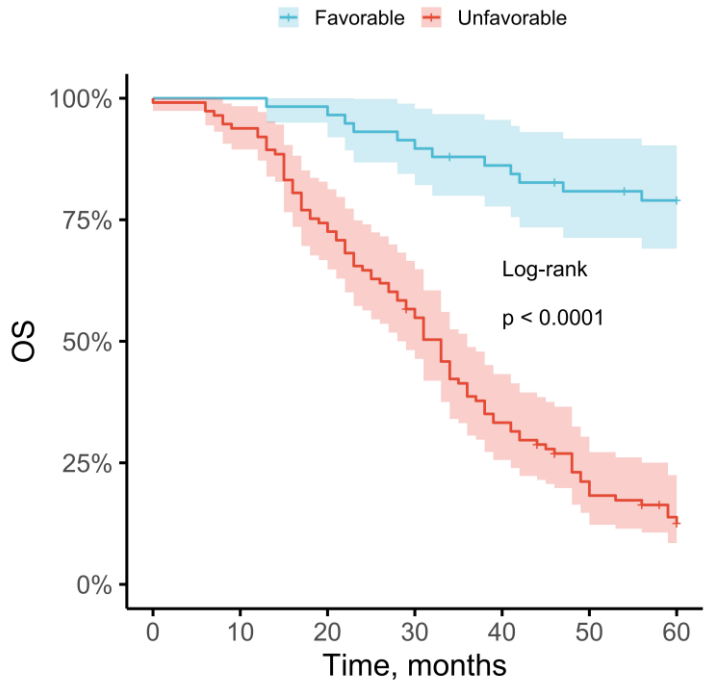
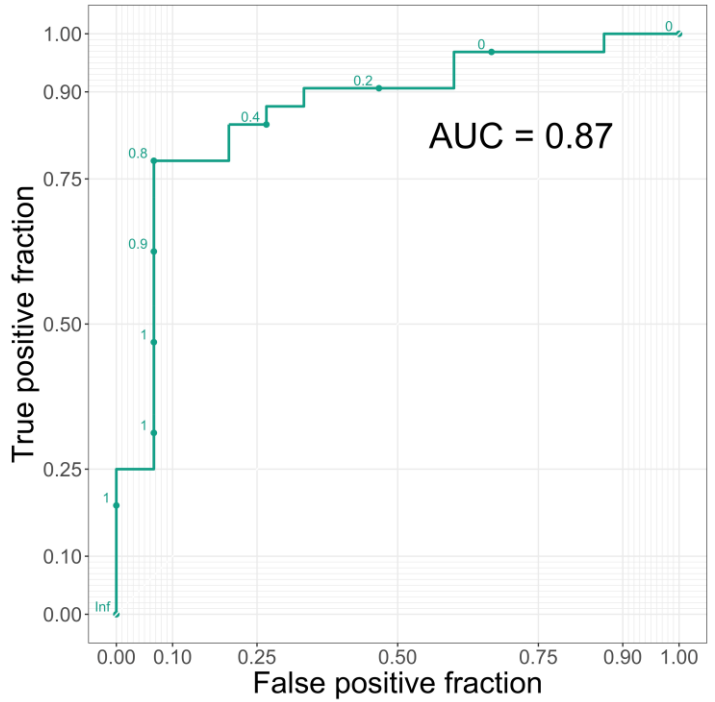

Favorable
Unfavorable
100%
75%
50%
25%
0%
OS
Log-rank
p < 0.0001
0
10
20
30
40
50
60
Time, months


AUC = 0.87
True positive fraction
False positive fraction
1.00
0.90
0.75
0.50
0.25
0.10
0.00
0.00
0.10
0.25
0.50
0.75
0.90
1.00

Спасибо за внимание!